INVESTIGATIONS IN THE FIELD OF N-ARYL-β-AMINO ACIDS

V. HYDRAZIDES OF N-ARYL-β-ALANINES

Z. F. Solomko, M. S. Malinovskii,
and V. T. Braichenko

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A series of works [1-4] has been devoted to the study of hydrazides of amino acids. Hydrazides of glycine, serine, and other amino acids possess bactericidal properties and display a high activity against staphylococci and streptococci bacteria [5, 6].

Hydrazides of β-amino acids are studied less. In this research hydrazides of N-aryl-β-alanines (I) were obtained from methyl esters of β-arylaminopropionic acids (Table 1). Hydrazides (I) were transformed into dihydrochlorides and into hydrazones (II) (Table 2). The dihydrochlorides are also formed upon reaction of hydrazones of acetone [(II), $R = R' = CH_3$] with hydrogen chloride. The main hydrolysis products of hydrazides (I) in basic medium are β-arylaminopropionic acids. An attempt to convert hydrazides (I) by the usual method [7] into 1,3,4-oxadiazoles (III) was not successful: N^1 = (N-phenyl-β-alanyl)-N^2-benzoylhydrazine was obtained under the indicated conditions. Cyclic products (III) were obtained from the hydrochlorides of methyl imino esters of (I).

Examinations carried out at the Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry showed that dihydrochlorides of hydrazides of N-phenyl-, N-p-tolyl-, N-m-tolyl-, and N-p-methoxyphenyl-β-alanine in a dilution of 1:8000 possess weak bacteriostatic activity in relation to acid-resisting bacteria, while the hydrazide of N-o-tolyl-β-alanine possesses germistatic activity in relation to the majority of the examined microorganisms.

EXPERIMENTAL

Hydrazides of N-Aryl-β-Alanines (I). We dissolved 0.01 mole of the methyl ester of (I) in 10 ml of alcohol and added a twofold excess of 25% hydrazine hydrate. The mixture was heated for 1 h with boiling of the alcohol and maintained for 12 h; the alcohol was distilled in vacuum until a dry residue was obtained, which was washed with ether, dried, and recrystallized from the appropriate solvent (see Table 1).

N-Phenyl-β-Alanine. We heated 1 g of (I) (X = H) for 3 h with a 10% solution of potassium hydroxide, neutralized the mixture with hydrochloric acid, extracted the mixture with ether, and obtained N-phenyl-β-alanine in 90% yield, mp 57-58° (from chloroform with petroleum ether) [8].

N^1-(N-Aryl-β-Alanyl)-N^2-Isopropylidenehydrazines [(II), $R = R' = CH_3$]. We boiled 0.01 mole of (I) for 30 min with 30 ml of dry acetone, distilled the acetone, and recrystallized the solid residue from a small amount of acetone (see Table 2).

Dihydrochlorides of Hydrazides (I). a. We dissolved 1 g of hydrazide (I) with 1.5 ml of hydrochloric acid, maintained the mixture for 24 h in a vacuum desiccator, and recrystallized the product from alcohol.

b. To absolute ethanol saturated with dry hydrogen chloride was added (II) ($R = R' = CH_3$) and the mixture was stirred until solution. The salt precipitates upon standing.

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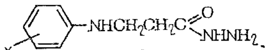
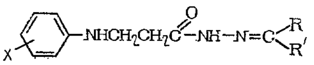
TABLE 1. Hydrazides of N-Aryl-β-Alanines



I

X	Yield, %	Mp (deg)	Found N, %		Calc. N, %	Dihydrochlorides				
						mp (deg)	found, %		calc., %	
							N	Cl	N	Cl
H	99,0	94—95	23,10 23,11	$C_9H_{13}N_3O$	23,40	191—192	16,64 16,51	27,71 27,62	16,60	28,16
p-CH_3O	82,0	126—127	20,28 19,98	$C_{10}H_{15}N_3O_2$	20,09	185—186	14,90 14,70	24,50 24,52	14,88	25,17
p-CH_3	80,6	135—136	21,40 21,55	$C_{10}H_{15}N_3O$	21,70	202—203	15,38 15,61	26,60 26,20	15,79	26,69
m-CH_3	67,3	115—116	21,55 21,63	$C_{10}H_{15}N_3O$	21,70	204—205	15,68 15,50	26,60 26,32	15,79	26,69
o-CH_3	72,4	129—130	22,00 21,87	$C_{10}H_{15}N_3O$	21,70	206—207	15,80 15,60	26,53 26,47	15,79	26,69
p-Cl	99,0	176—177	20,04 19,77	$C_9H_{12}ClN_3O$	19,67	192—193	14,90 14,70	36,50 36,65	14,65	36,84
o-NO_2	90,0	103—104	25,38 25,15	$C_9H_{12}N_4O_3$	25,00	—	—	—	—	—
p-NO_2	90,0	147—148	25,20 25,17	$C_9H_{12}N_4O_3$	25,00	—	—	—	—	—
2-NH_2, 4NO_2	81,00	162—163	28,90 28,72	$C_9H_{13}N_5O_3$	29,28	—	—	—	—	—

TABLE 2. Hydrazones



II

X	R	R′	Yield, %	Mp (deg)	Found, N, %	Empirical formula	Calc., N, %
H	CH_3	CH_3	90,00	124—125	19,10 19,40	$C_{12}H_{17}N_3O$	19,17
p-CH_3	CH_3	CH_3	92,0	78—79	18,00 17,67	$C_{13}H_{19}N_3O$	18,02
p-CH_3	CH_3	CH_3	89,5	118—119	17,98 17,88	$C_{13}H_{19}N_3O$	18,02
m-CH_3	CH_3	CH_3	90,5	99—100	17,95 18,22	$C_{13}H_{19}N_3O$	18,02
p-Cl	CH_3	CH_3	98,0	126—127	16,87 16,43	$C_{12}H_{16}ClN_3O$	16,50
p-CH_3O	CH_3	CH_3	95,5	107—108	16,72 16,55	$C_{13}H_{19}N_3O_2$	16,80
o-NO_2	CH_3	CH_3	98,0	148—149	21,00	$C_{12}H_{16}N_4O_3$	21,20
H	H	$C_6H_2N(CH_3)_2$-p	84,0	172—173	18,48	$C_{18}H_{22}N_4O$	18,06
p-CH_3	H	$C_6H_4N(CH_3)_2$-p	98,0	164—165	17,03	$C_{19}H_{24}N_4O$	17,30
o-CH_3	H	$C_6H_4N(CH_3)_2$-P	98,0	155—156	16,98	$C_{19}H_{24}N_4O$	17,30
p-CH_3O	H	$C_6H_4N(CH_3)_2$-P	95,0	166—167	16,34	$C_{19}H_{24}N_4O_2$	16,46
o-NO_2	H	$C_6H_4N(CH_3)_2$-P	93,0	160—161	20,74	$C_{18}H_{21}N_5O_3$	20,30

N^1-(N-Aryl-β-alanyl)-N^2-(p-dimethylaminobenzylidene)hydrazines [II, R = H, R′ = $C_6H_4N(CH_3)_2$ = p]. We dissolved 0.01 mole of (I) and 0.012 mole of p-dimethylaminobenzaldehyde in 50 ml of ethanol, acidified the mixture to pH 4.0 with acetic acid, and boiled it for 1 h. The solution was filtered and water was added to it. During this a precipitate appears.

N^1-(N-Phenyl-β-alanyl)-N^2-benzoylhydrazine. We dissolved 0.01 mole of (I) (X = H) in dry pyridine and added dropwise with stirring 0.01 mole of benzoyl chloride. The reaction mass was stirred for 40 min and poured into cold water; the precipitate was filtered and washed with water and alcohol until absence of a pyridine odor. Yield 60%, mp 225-226° (from alcohol). Found %: C 67.52; H 5.82; N 14.87. $C_6H_{17}N_3O_2$. Calculated %: C 67.80; H 6.00; N 14.84.

2-(N-o-Tolyl-β-aminoethyl)-5-phenyl-1,3,4-oxadiazole (IIIa). A mixture of 0.03 mole of benzhydrazide and 0.03 mole of the hydrochloride of the methyl imino ester of o-toluidinopropionic acid in 20 ml of dry pyridine was heated for 2 h and after cooling the reaction mass was poured into water. The precipitate was filtered, dried, and recrystallized from alcohol. Yield 53.7%, mp 135-136°. Found %: C 73.38; H 6.09; N 15.18. $C_{17}H_{17}N_3O$. Calculated %: C 73.11; H 6.00; N 15.05.

2-(N-m-Tolyl-β-aminoethyl)-5-phenyl-1,3,4-oxadiazole (IIIb). The material was obtained analogously to (IIIa) from 0.03 mole of benzhydrazide and 0.033 mole of the hydrochloride of the methyl imino ester of m-toluidinopropionic acid. Yield 70.7%, mp 88-89°. Found %: C 73.11; H 6.09; N 15.3. $C_{17}H_{17}N_3O$. Calculated %: C 73.11; H 6.00; N 15.05.

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